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EXAMINER	
FOSTER, CHRISTINE E	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/022,481	SALES AMILL ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-8,10-18,22,32,34 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-8,10-18,22,32,34 and 35* is/are rejected.

7)☒ Claim(s) *14,15 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/18/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 1/24/08, is acknowledged and has been entered. Claims 1, 10, 14, 15-18, 22, 32, and 34-35 were amended. Claims 2, 9, and 20 were canceled. Accordingly, claims 1, 3, 5-8, 10-18, 22, 32, and 34-35 are currently pending and subject to examination below.

Objections/Rejections Withdrawn

2. The claim objections set forth in the previous Office action are withdrawn in response to Applicant's amendments.

3. The rejections of claims 2, 9, and 20 are moot in light of Applicant's cancellation of the claims.

4. The rejections under § 112, 2nd paragraph not reiterated below have been withdrawn.

5. The rejections of claims 1-3, 5-7, and 10-12 under § 102(b) as being anticipated by David et al. are withdrawn in response to Applicant's amendments to incorporate the limitations of claim 9 (now cancelled) into the independent claim.

Claim Objections

6. Claims 14-15 and 17 are objected to because of the following informalities:

7. Claim 17 (as instantly amended) recites that "molar ratio of the third member **and** the unbound form of the first member in the sample is between about 10 and 40" (emphasis added). It appears that Applicant intends that the ratio of the third member to the second member is being

conveyed (Reply, page 9). However, the wording of the claim may present confusion because it is ambiguous as to what the ratio is referring to, i.e. the ratio of the third member to the first member or alternatively the ratio of the first member to the third member. In other words, it is unclear which of the members is present in the higher amount.

Similarly, claims 14-15 present similar issues since they refer to the ratio of two species but do not make clear which of the species is in the greater quantity.

Applicant is requested to clarify the language of the claims in order to make clear that the molar ratios recited refer to the molar ratios of the first recited species **to** the second recited species.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 3, 5-8, 10-18, 22, 32, and 34-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.*

10. Claim 3 recites that at least one of the particles "**comprises**" latex (see the amendment of 8/4/04). As originally filed, the claim recited that the first and/or second particle "**is**" latex". This

amendment broadens the scope of the original claim to include not only latex particles but also particles that include latex as well as additional components. Support for this broadening amendment drawn to particles that "comprise" latex (rather than particles that *are* latex) could not be found in the specification.

11. Claims 8 and 18 now recite that the first member "**comprises**" Protein S (see the amendment of 4/15/05). Claims 8 and 19 as originally filed recited that the first member "**is**" protein S (the limitations of claim 19 have now been incorporated into claim 18).

The amendments broaden the scope of the claims, since second members that "comprise" Protein S would include not only Protein S *per se* but also polypeptides having an unlimited number of additional amino acids and/or additional components in addition to the Protein S sequence, e.g. fusion proteins, modified forms, etc. The disclosure of Protein S *per se* fails to convey evidence of possession of the claimed members that *comprise* Protein S but which may include other additional components or amino acid sequences.

12. Similarly, claim 1 (as instantly amended) recites a second member "**comprising** C4b-binding protein (C4BP) or a fragment of C4BP that binds to protein S" (see also the amendment filed 4/15/05). Claim 18 also recites a second member that "**comprises** C4b-binding protein (C4BP) or a fragment of C4BP that binds to protein S".

The specification and claims as originally filed disclose a second member that "**is**" C4BP. Likewise, claims 9 and 19 as originally filed recited that the second member "is" C4BP. The amendments of 4/15/05 introduced the limitations that the second binding member "**comprises**" C4BP **or a fragment thereof**. The current use of open transitional language conveys a difference in scope, since second members that "comprise" C4BP would include polypeptides having an

unlimited number of additional amino acids and/or additional components in addition to C4BP, e.g. fusion proteins, modified forms, etc. As such, the claims broaden the scope of the original disclosure, and therefore represent new matter. The disclosure of C4BP *per se* fails to convey evidence of possession of the claimed members that *comprise* C4BP.

13. Claim 17 (as instantly amended) recites that "molar ratio of the third member and the unbound form of the first member in the sample is between about 10 and 40". As originally filed, the claim recited that "the molar ratio of third member is between about 10 and 40 times the amount of free first member in the sample". The amendments represent new matter because the claim is now ambiguous as to what the recited ratio refers to. In particular, the claim could be interpreted to mean either that the ratio of third member to first member is 10-40, or alternatively that the ratio of first member to third member is 10-40. These are mutually exclusive scenarios (in the first case, the third member is present in a higher amount, while in the second case, the first member is present in a higher amount). However, only the former is disclosed in the specification (see [0069]). Because the claim could now be interpreted as referring to the use of 10-40X more first binding agent than third binding agent (which is not described in the specification) the claim as amended represents new matter.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 1 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

16. Claim 1 recites the limitation "the sample" in lines 10 and 19. There is insufficient antecedent basis for this limitation in the claim because the claim previously recites both "a sample containing both the unbound form and a bound form of the first member" (preamble) as well as "a sample" in line 6, and there is no requirement that these samples are one and the same. Therefore, there is ambiguity as to which sample is meant by "the sample".

17. Claim 22 recites the limitation "the single binding site to which the second member binds". There is insufficient antecedent basis for this limitation in the claims since there is no prior mention that the second member (C4BP or a fragment thereof) binds to a single binding site.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 1, 3, 5-8, 10-12, 18, 22, 32, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over David et al. (US 4,486,530) in view of Giri et al. (Thromb Haemost. 1998 Apr;79(4):767-72).

David et al. teach two-site or sandwich immunometric assay techniques for the determination of a first member ("antigenic substance" or "antigen") in a sample (the abstract and column 4, line 50 to 5, line 10; and column 6, line 54 to column 7, line 7, line 2). In particular, the reference teaches assay formats where a first quantity of particles to which a

second member ("first monoclonal antibody") is bound is mixed with a second quantity of particles to which a third member ("second monoclonal antibody") is bound (column 9, line 58 to column 10, line 41). When a sample containing the antigen is introduced, agglutination of the particles occurs to form easily detectable particle clumps, which can be used to determine the presence of the antigen, e.g. by detecting the change in turbidity by nephelometry (column 9, line 68 to column 10, line 41). David et al. make clear that agglutination causes an *increase* in turbidity (see also column 15, lines 52-63). With respect to the limitation that an "unbound form" of the first member is detected, given the broadest reasonable interpretation of such terminology, the teaching in David et al. in which the antigen in the sample is initially not bound to the detection antibodies reads on the claims since the antigen would be considered to be in a form that is not bound to the detection antibodies, i.e. an unbound form.

David et al. therefore teaches methods for determination of a first member substantially as claimed in a sandwich-type latex agglutination assay using two monoclonal antibodies as second and third members.

The teachings of David et al. differ from the claimed invention in that it fails to specifically teach that the second member comprises C4BP or a protein S-binding fragment thereof. Regarding claim 8, David et al. also fails to specifically teach that the first member detected is protein S.

Giri et al. teach that free (unbound) protein S antigen is active as a cofactor to APC and is present at low levels in individuals with protein S deficiency (see in particular the abstract and page 767, the paragraph bridging the left and right columns). The reference further teaches that measurement of free protein S (as compared to total protein S) in plasma has superior predictive

value for protein S deficiency, which is related to thrombophilia (page 767, right column, first full paragraph). As such, assays for free protein S are useful for routine clinical purposes to detect protein S deficiencies (the abstract).

The reference also teaches that C4BP (the natural ligand of protein S) and a monoclonal anti-protein S antibody HPS 54 can be used as binding agents to assay specifically for free protein S in a sandwich or two-site assay (see especially page 767, right column, the second full paragraph; page 768, left column; and page 771, "Discussion"; and page 772, the last paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to detect free protein S as the antigen in the method of David et al. One would be motivated to do this because Giri et al. teach that free protein S is associated with disease, and that detection of this antigen can be used for routine clinical purposes to detect protein S deficiencies, which are related to thrombophilia.

Furthermore, in light of the teachings of Giri et al. that free protein S can be successfully detected using it natural ligand C4BP, it would have been further obvious to substitute C4BP as the second member in place of the monoclonal antibody taught by David et al., for the same purpose of detecting free protein S because it is obvious to select a known material for their known purpose and obtain the expected results. In addition, one would also be motivated to employ C4BP as the second member in the method of David et al. and Giri et al. because Giri et al. teach that the interaction between protein S and C4BP is very stable (page 771, left column, the fourth paragraph). Furthermore, using CRBP results in an assay that is not influenced by C4BP-protein S complexes (bound form of protein S) or other factors present in plasma (page 771, left column, the last full paragraph).

Regarding the recitation in the preamble of a sample "containing both the unbound and a bound form of the first member", it is noted that the body of the claim does not clearly require such a sample. As such, the preamble statement may be interpreted as merely stating the purpose or intended use of the invention and does not necessarily further limit the claimed invention. MPEP 2111.02.

Nonetheless, Giri et al. teaches detection of free protein S in plasma (abstract; page 768, left column, the sections "Two-step procedure" and "One-step procedure; and right column, last paragraph), which is the same sample type disclosed instantly [0068]. Therefore, it would have been further obvious to use the assay format of David et al. to detect free protein S in plasma given the teachings of Giri et al. that plasma detection of free protein S is a useful means of clinically assessing protein S deficiency.

With respect to the product claims, it would have been further obvious to provide the necessary reagents for performing the method of David et al. and Giri et al. together in composition or kit form for the well-known advantages of convenience, economy, and/or commercial sale.

One would have a reasonable expectation of success because the teachings of Giri et al. establish that it is possible to determine free protein S in a sandwich-type assay format using C4BP and a monoclonal antibody. Furthermore, one would have had a reasonable expectation of success in employing the particle-based assay format of David et al. to detect the free protein S antigen taught by Giri et al. because David et al. indicates that the method can be used to detect a wide variety of antigens (column 5, line 55 to column 6, line 2).

With respect to the limitation that the second and third members bind to different sites, Giri et al. teach that C4BP and the anti-protein S monoclonal antibody bind to different sites on protein S since they do not interfere with each other (page 767, right column, the second full paragraph). David et al. also teach that the two antigen-specific reagents should bind to different sites (see for example column 4, lines 50-68). The C4BP and the anti-protein S monoclonal antibody taught by Giri et al. do not bind to each other since the antibody is specific for protein S and not for C4BP.

With respect to claim 3, David et al. teach latex particles (column 10, lines 42-45).

With respect to claims 5-6, David et al. teach that because the second and third members do not interfere with the binding of each other to the antigen, such that both are necessary for formation of the sandwich, both reverse and simultaneous assays can be conducted (column 6, lines 54-67). Simultaneous assays involve a single incubation step in which both antibodies are added to the sample at the same time (in which case steps (a)-(d) would be performed simultaneously), while reverse assays involve stepwise (i.e., sequential) addition of the antibodies (see column 2, lines 34-55).

With respect to claim 7, David et al. teach determining the amount of antigen present in the sample (column 10, lines 37-41).

With respect to claim 10, David et al. teach serum (column 1, lines 13-15).

With respect to claims 11-12, Giri et al. teaches C4BP and protein S as second and first members, respectively. Since these are the same proteins disclosed instantly, they would also possess the recited binding properties. The antibody of Giri et al., as a monoclonal antibody, would bind at a single binding site. The antibody binds to protein S at a different site than C4BP

since it did not interfere with protein S binding (abstract). Therefore, when performing the method of David et al. and Giri et al. as discussed above, the indicated features would necessarily follow.

With respect to claim 22, the anti-protein S antibody of Giri et al., as a monoclonal antibody, would bind to a single site or epitope.

With respect to claim 32, Giri et al. teach comparing the amount of C4BP-free protein S-antibody complex formed with the amount in healthy controls (see especially Table 3). As discussed above, the reference also teaches that determination of free protein S can be used to detect protein S deficiencies, which are associated with thrombophilia (see especially page 767, right column). Given the known association with disease, it would have been obvious to compare free protein S levels (as indicated by detection of the amount of second complex) with those of healthy controls as was done by Giri et al. One would be motivated to do this in order to distinguish disease and control subjects. Furthermore, given that protein S deficiencies are associated with thrombophilia, it would have been further obvious to diagnose thrombophilia (or tendency to develop thrombosis) in those subjects found to have protein S deficiencies as measured by low levels of free protein S, given the teachings of Giri et al. that protein S deficiencies are associated with venous thrombosis.

With respect to claim 34, David et al. teach that the latex particles vary in size between about 0.2 to about 10 microns, which overlaps the instantly claimed range (column 10, lines 42-50). In such a case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. MPEP 2144.05.

20. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over David et al. in view of Giri et al. as applied to claim 1 above, and further in view of Ballas et al. (US 4,812,395).

David et al. and Giri et al. are as discussed above, which teach methods for determination of a first member (protein S) substantially as claimed, but which fail to specifically teach that step (b) is performed within 0 to about 180 seconds.

However, such time periods were disclosed in the prior art in the context of performing agglutination assays. For example, Ballas et al. teach a particle agglutination method in which a particulate reagent is added to the sample and signal is detected 29-46 seconds afterwards (which is a range that is encompassed by that recited in claim 13; see column 19, lines 27-46).

Therefore, it would have been obvious to one of ordinary skill in the art to perform the claimed step within the recited time periods in the course of routine optimization, out of the normal desire of artisans to improve upon what is already known. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (see MPEP 2144.05).

21. Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over David et al. in view of Giri et al. as applied to claim 1 above, and further in view of Mischak et al. (US 6,124,430).

David et al. and Giri et al. are as discussed above, which teach methods for determination of a first member (protein S) substantially as claimed, but which fail to specifically teach the

specific molar ratios of the reagents used in the assay, and fail to specifically teach that the third member is present in higher amount than the free member in the sample.

Mischak et al. teaches that in a sandwich-type assay, antibody is typically used in amounts substantially higher than the amount of analyte expected in the sample (see especially column 8, lines 7-10).

Therefore, it would have been obvious to employ an excess of antibody (third member) in the method of David et al. and Giri et al. as taught by Mischak et al. One would be motivated to do this in order to successfully detect analyte, in light of the teachings of Mischak et al. that an excess of antibody is normal practice when performing sandwich-type assays, such as that of David et al. and Giri et al.

It would have been further obvious to select concentrations of the reagents for the assay within the claimed molar ratios in the course of routine optimization, out of the normal desire of artisans to improve upon what is already known. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (see MPEP 2144.05).

22. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over David et al. in view of Giri et al. as applied to claim 18 above, and further in view of Cambiaso et al. (US 4,184,849).

David et al. and Giri et al. are as discussed above, which teach a composition or kit for detecting free protein S in a dual particle sandwich-type latex agglutination assay. However, the references fail to specifically teach that the sizes of the first and second particles are different.

Cambiaso et al. teach agglutination assays using two particles (see especially the abstract). The reference teaches that the extent of agglutination can be detected using selective counting techniques, in which case it is highly advantageous that the two particles be of a different size so that they may be distinguished by the counter (column 3, line 44 to column 4, line 37). Such particle counting techniques avoid the need for separation steps, which are time-consuming and may introduce error (column 3, lines 55-65).

Therefore, it would have been obvious to one of ordinary skill in the art to employ first and second particles of different size, as taught by Cambiaso et al., in the composition or kit of David et al. and Giri et al. One would be motivated to do this in order to detect agglutination in the method of David et al. and Giri et al. using a particle counter, which obviates the need for a separation step.

Double Patenting

23. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

24. Claims 1, 3, 5-8, and 10-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,379,975 in view of David et al.

The '975 patent claims a method for determining the level of a first member (free protein S) by contacting a second member ("ligand") that may be C4BP (and which may be linked to a carrier) with the sample (see especially claims 1-2 and 6-7). Detection may be via a third member (antibody specific for protein S) (see claim 5).

The patent claims differ from the instantly claimed invention in that they do not recite detection by an increase in the turbidity of the sample as a result of particle agglutination. Although in the '975 patent the C4BP may be linked to a carrier, the carrier is not specifically recited to be a particle. Furthermore, the third member (antibody) is not bound to a particle.

However, sandwich-type assay formats employing two particles were known in the art. David et al. (discussed further above) teach two-site or sandwich immunometric assay techniques for the determination of a first member ("antigenic substance" or "antigen") in a sample (the abstract and column 4, line 50 to 5, line 10; and column 6, line 54 to column 7, line 7, line 2). In particular, the reference teaches assay formats where a first quantity of particles to which a second member ("first monoclonal antibody") is bound is mixed with a second quantity of particles to which a third member ("second monoclonal antibody") is bound (column 9, line

58 to column 10, line 41). When a sample containing the antigen is introduced, agglutination of the particles occurs to form easily detectable particle clumps, which can be used to determine the presence of the antigen, e.g. by detecting the change in turbidity by nephelometry (column 9, line 68 to column 10, line 41). David et al. make clear that agglutination causes an *increase* in turbidity (see also column 15, lines 52-63).

Therefore, it would have been obvious to one of ordinary skill in the art to perform the method of the '975 patent by immobilizing both C4BP and antibody on particles, in order to detect free protein S by the sandwich-type agglutination assay format of David et al. One would be motivated to do this in order to detect the amount of free protein S by nephelometric techniques.

25. Claims 1, 3, 5-8, 10-18, 22, and 34-35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-41 of U.S. Patent No. 7,041,458 in view of David et al.

The '458 patent claims kits for assaying free protein S employing second and third members (C4BP and an antibody for protein S) in a sandwich-type assay format (see especially claims 1 and 24). The second member may be immobilized on a carrier (claims 2-4).

However, the patent claims differ from the instantly claimed invention in that they fail to specifically teach that the second and third members are bound to particles, or that detection is via detection of a change in turbidity of the sample as in instant claim 1.

However, sandwich-type assay formats involving two particles were known in the art. David et al. (discussed further above) teach two-site or sandwich immunometric assay

techniques for the determination of a first member ("antigenic substance" or "antigen") in a sample (the abstract and column 4, line 50 to 5, line 10; and column 6, line 54 to column 7, line 7, line 2). In particular, the reference teaches assay formats where a first quantity of particles to which a second member ("first monoclonal antibody") is bound is mixed with a second quantity of particles to which a third member ("second monoclonal antibody") is bound (column 9, line 58 to column 10, line 41). When a sample containing the antigen is introduced, agglutination of the particles occurs to form easily detectable particle clumps, which can be used to determine the presence of the antigen, e.g. by detecting the change in turbidity by nephelometry (column 9, line 68 to column 10, line 41). David et al. make clear that agglutination causes an *increase* in turbidity (see also column 15, lines 52-63).

Therefore, it would have been obvious to one of ordinary skill in the art to immobilize both C4BP and antibody on particles in the kits of the '458 patent, in order to detect free protein S by the sandwich-type agglutination assay format of David et al. One would be motivated to do this in order to detect the amount of free protein S by nephelometric techniques.

26. Claim 32 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,379,975 in view of David et al. as applied to claim 8 above, or alternatively over claims 1-41 of U.S. Patent No. 7,041,458 as applied to claim 8 above, and further in view of Giri et al.

The teachings of the '975 and '458 patents are as discussed above, which fail to specifically teach diagnostic methods.

Giri et al. teach that free (unbound) protein S antigen is active as a cofactor to APC and is present at low levels in individuals with protein S deficiency (see in particular the abstract and page 767, the paragraph bridging the left and right columns). The reference further teaches that measurement of free protein S (as compared to total protein S) in plasma has superior predictive value for protein S deficiency, which is related to thrombophilia (page 767, right column, first full paragraph). As such, assays for free protein S are useful for routine clinical purposes to detect protein S deficiencies (the abstract).

Therefore, given the known association of protein S with disease, it would have been obvious to compare free protein S levels (as indicated by detection of the amount of second complex) with those of healthy controls as was done by Giri et al. One would be motivated to do this in order to distinguish disease and control subjects. Furthermore, given that protein S deficiencies are associated with thrombophilia, it would have been further obvious to diagnose thrombophilia (or tendency to develop thrombosis) in those subjects found to have protein S deficiencies as measured by low levels of free protein S, given the teachings of Giri et al. that protein S deficiencies are associated with venous thrombosis.

Response to Arguments

27. Applicant's arguments in the Reply filed 1/24/08 have been fully considered.

28. With respect to the rejection of claims 3, 8, 17-18, 22, 32, and 34-35 under § 112, 1st paragraph as containing new matter (now applied to claims 1, 3, 5-8, 10-18, 22, 32, and 34-35 above), Applicant's arguments have been fully considered but they are not persuasive. Applicant points to the case of Amgen, Inc. v. Hoechst Marion Roussel, Inc. (Reply, page 8, first full

paragraph). Regarding claim 3, Applicant further argues that support for a particle "comprising at least latex" can be found in paragraphs 54 and 67-69 of the specification. Regarding claims 8 and 18, Applicant further argues that support may be found at paragraph 33 and 52.

This is not found persuasive because the facts of Amgen, Inc. v. Hoechst Marion Roussel, Inc. differ from the instant case. Initially, the Examiner notes that in the passage indicated by Applicant, the court is specifically referring to claimed *products*, in particular to a claimed composition. No relevance can be seen for the instant method claims under examination such as claims 3 and 8.

Furthermore, the passage indicated by Applicant relates to issues of *enablement*, which is not found relevant since the rejections pertain to the *written description* requirement. Similarly, Applicant's arguments that the specification, figures and claims as originally filed provide sufficient description to enable one of skill in the art to carry out at least one mode of the claimed composition (Reply, page 8) are not found relevant to the instant new matter rejections.

Regarding claim 3, the examiner has reviewed the various specification passages indicated by Applicant but was unable to find support for the genus of particles that "comprise" latex (but which may include other ingredients or components). Therefore, it is maintained for reasons of record that the claim represents a broadening amendment since the disclosure of latex particles *per se* does not adequately describe particles that *comprise* latex.

Regarding claims 8 and 18, the passages indicated by Applicant were previously considered by the Examiner as indicated in the prior Office action (see the Office action mailed 7/24/07 at page 5, item 17); however, for reasons of record support could not be found therein for a method as claimed wherein the first member "comprises" Protein S. The specification fails

to convey evidence of possession methods of detecting unbound forms of all members "comprising" Protein S in a sample, as only protein S *per se* is described with any particularity.

Applicant's reply does not apparently include specific arguments relating to the rejections of claims 9 and 18 as containing new matter in reciting that the second member "comprises" C4BP or a fragment thereof.

29. Applicant's arguments with respect to the recitation of a "fragment of C4BP that binds protein S" (Reply, pages 8-9) are persuasive to obviate this aspect of the rejection.

30. With respect to the rejection of claim 17 under § 112, 1st paragraph, Applicant argues that the claim has been amended to clarify that the sample contains "a molar ratio of the third member **to** the first member of between about 10 and 40" (Reply, page 9; emphasis added). The Examiner agrees that such language is supported by the original specification. However, the rejection is maintained for reasons of record because the claim recites a "molar ratio of third member **and** the unbound form of the first member", which is ambiguous because it does not make clear which member is present in the greater quantity.

31. With respect to the rejection of claim 22 under § 112, 2nd paragraph, Applicant's reply does not apparently include specific arguments relating to the rejection, which is maintained for reasons of record.

32. Applicant's arguments with respect to the rejections under § 102 have been considered (see Reply, pages 10-11) but are moot in view of the new ground(s) of rejection.

33. With respect to the rejections under § 103(a) as being unpatentable over David et al. in view of Giri et al., Applicant's arguments (see pages 12-13) have been fully considered but are not persuasive of error.

Applicant argues that David only teaches the use of two monoclonal antibodies, and neither teaches nor appreciates the use of a binding partner other than an antibody to detect an antigen in a two-site assay. Applicant further argues that David does not teach or suggest detecting an unbound form of a binding pair in a sample that contains both unbound and bound forms. Applicant further argues that Giri teaches an ELSA assay rather than a method involving turbidity, and urges that ELSA is time consuming, difficult, and expensive to automate. See Reply, page 12.

This is not found persuasive because it amounts to a piecemeal analysis of the references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the instant case, the Giri reference has been relied on for its teaching of detecting free (unbound) protein S antigen through the use of its natural ligand C4BP as a binding partner; while the teaching of a turbidimetry assay is found in David et al.

Applicant further argues that Giri does not teach or suggest that the method may be used to detect an unbound form of a binding pair *in a sample in the presence of both bound and unbound forms* (Reply, page 12). In particular, Applicant argues that the ELSA method of Giri requires separation of bound and unbound forms of protein S, either during the preanalytical step, by polyethylene glycol precipitation or by washing (Reply, see the paragraph bridging pages 12-13). Applicant points to Giri at page 768, left column.

It is not entirely clear what "preanalytical step" is meant by Applicant since a number of experimental steps are detailed on page 768, left column. If Applicant is referring to the teaching in Giri at page 768, left column, "Proteins", in which protein S bound to C4BP was removed, the examiner notes that this is in a different context and does not relate to the **sample** being assayed by the method. In particular, it is important to note that this purification step was not performed on the sample being assayed. Rather, it was in preparing purified C4BP for use as the capture reagent, just as disclosed instantly [0061]. Therefore, this passage in Giri says nothing about the **sample** being assayed by the method.

Regarding the polyethylene glycol precipitation mentioned by Applicant, no teaching of PEG precipitation could be found where indicated by Applicant on page 768, left column of Giri. Giri does mention PEG precipitation at page 767, right column, first full paragraph; but this is in pointing out the disadvantages of prior art methods. PEG precipitation is also mentioned by Giri at page 768, right column, "Characterization of the Assay", but it is mentioned in the context of a different, in-house radioimmunoassay that was performed for the purposes of comparison.

In response to applicant's argument that the ELSA method of Giri includes washing away the complex that does not bind to the solid phase, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, the elimination of washing steps is specifically taught as one of the advantages of the assay format of David et al. (column 2). Therefore, Applicant's

arguments are not persuasive inasmuch as they focus on the teachings of the individual references, and not what the prior art as a whole would suggest to the ordinary artisan.

Giri makes clear that the assay was performed using plasma samples, which is the same sample type disclosed instantly (see especially page 768, left column, "Two-step procedure; "One-step procedure"; right column; last paragraph), and therefore reads on a sample containing both bound and unbound forms.

Applicant's arguments for disadvantages of the ELSA assay format of Giri et al. and for the solution of an unmet need and commercial advantage of the instant method (Reply, pages 12-13) have been considered but are not seen as evidence of unexpected results. Applicant is reminded that such evidence should be factually supported by appropriate affidavit or declaration to be of probative value (MPEP 716.01(c) and 716.02(g)). The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965).

Whether evidence shows unexpected results is a question of fact and the party asserting unexpected results has the burden of proving that the results are unexpected. In re Geisler, 116 F.3d 1465, 1469-70, 43 USPQ2d 1362, 1364-5 (Fed. Cir. 1997). The evidence must be (1) commensurate in scope with the claimed subject matter, In re Clemens, 622 F.2d 1019, 1035, 206 USPQ 289, 296 (CCPA 1980), (2) show what was expected, to "properly evaluate whether a … property was unexpected", and (3) compare to the closest prior art. Pfizer v. Apotex, 480 F.3d 1348, 1370-71, 82 USPQ2d 1321, 1338 (Fed. Cir. 2007).

In the instant case, the evidence of record indicates that the advantages of turbidimetric assay formats (such as that of David et al.) were known in the art. For example, David et al.

explicitly teach that the need for washing steps and lengthy incubation steps is eliminated by their assay format (see column 2). Therefore, when using the assay format of David et al. in order to detect free protein S, reduction in steps and time would in fact be *expected*. Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." In re Gershon, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967).

Lastly, the allegations of unexpected results are not commensurate with the scope of the claims, which are not limited to detection of unbound protein S but rather are drawn to all "first members".

34. With respect to the rejection of claim 13 under § 103, Applicant does not separately argue the limitations of the dependent claim (Reply, pages 13-14).

35. With respect to the rejections of claims 14-17 under § 103, Applicant argues with respect to claims 14-15 that Mishak does not teach or suggest modifying the molar ratios of two binding partners (Reply, page 14). This is not found persuasive because no evidence of criticality has been advanced. The teachings of Mishak establish that antibody concentration (i.e., third member) was known in the art to be a result-effective variable. As such, absent evidence of criticality it is maintained that it would have been obvious to arrive at the claimed invention out of the course of routine optimization.

36. With respect to the rejection of claim 35 under § 103, Applicant argues that Cambiaso teaches a mixed agglutination assay (Reply, page 15), which is not found persuasive because it amounts to a piecemeal analysis of the references. The test for obviousness involves consideration of what the combined teachings, as opposed to the individual teachings, of the

references would have suggested to those of ordinary skill in the art. In re Young, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991); In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981).

37. With respect to the rejections on the grounds of nonstatutory obviousness-type double patenting over U.S. 6,379,975 and U.S. 7,041,458, Applicant advances a statement as to a joint research agreement involving these patents and submits that neither of these patents is available as prior art (Reply, page 16). This is not found persuasive because while statements regarding joint research agreements may overcome a rejection under 35 U.S.C 103(a), the rejections at issue relate to double patenting. Therefore, the rejections are maintained for reasons of record.

Conclusion

38. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Primary Examiner, Art Unit 1641

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